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Vivarium Lighting as an Important Extrinsic Factor Influencing Animal-based Research

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Light is an extrinsic factor that exerts widespread influence on the regulation of circadian, physiologic, hormonal, metabolic, and behavioral systems of all animals, including those used in research. These wide-ranging biologic effects of light are mediated by distinct photoreceptors, the melanopsin-containing intrinsically photosensitive retinal ganglion cells of the nonvisual system, which interact with the rods and cones of the conventional visual system. Here, we review the nature of light and circadian rhythms, current industry practices and standards, and our present understanding of the neurophysiology of the visual and nonvisual systems. We also consider the implications of this extrinsic factor for vivarium measurement, production, and technological application of light, and provide simple recommendations on artificial lighting for use by regulatory authorities, lighting manufacturers, designers, engineers, researchers, and research animal care staff that ensure best practices for optimizing animal health and wellbeing and, ultimately, improving scientific outcomes.

Abbreviations: bLAD, blue-enriched LED light at daytime; Clock, circadian locomotor output kaput; CCT, correlated color temperature; CWF, cool white fluorescent; ipRGC, intrinsically photosensitive retinal ganglion cell; HIOMT, hydroxyindole-*O*-methyltransferase; LAN, light at night; LED, light-emitting diode; PLR, pupillary light reflex; SCN, suprachiasmatic nuclei; SPD, spectral power distribution

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Introduction

An extrinsic factor in animal-based research is an environmental feature like noise, temperature, vibration and humidity. Like these, light is a fundamental extrinsic factor that should be considered in the design and operation of animal research facilities. The profound effect of light on circadian behavior and physiology is well established.[61,78-85,114,151,161,175,207,221,239,251,265-268,294,307,320,322,364] During the past 3 decades, empirical evidence has shown that all life varies in a species-specific manner in the capacity to use visible and nonvisible photic energy.[137] Light supports vision that allows animals to see and navigate their surroundings, but light also functions below the level of consciousness, regulating a range of metabolic and physiologic responses that oscillate with a 24-h rhythm throughout the day (i.e., circadian rhythm).[43] Minor alterations in light intensity,[39] spectral quality,[37] and duration[38] at a given time of day can alter or disrupt the circadian regulation of neuroendocrine, neurobehavioral, metabolic, and physiologic parameters that are associated with animal health and wellbeing and, ultimately, scientific outcomes. Locomotor activity and sleep are the behaviors with the most obvious circadian rhythms. However, hormones (including melatonin, corticosterone, and insulin), core body temperature in endotherms, metabolism, immune function, and many other metabolic, physiologic, and behavioral processes also have rhythms that are regulated by the light–dark cycle.[77,81,84,127,177,264,284,286,350,352,365] Inaccurate measurement and reporting of light and inappropriate species-specific lighting protocols in an animal facility may present both a potential source of unrecognized animal distress and a significant confounding variable in scientific studies, thus undermining the 3Rs of refining animal models and reducing the numbers of animals used in biomedical research,[79,102,137] while also compromising reproducibility, transparency, and accountability in research studies.[63]

Artificial light emitted by a variety of current lighting technologies has a substantial influence on neurobehavioral and neurophysiological responses in research animals.[77,79,118,205,206] Light is the most influential and potent regulator of circadian clocks, and circadian rhythmicity is an integrating feature of nearly every physiologic, metabolic, and behavioral system that brings a multitude of biologic processes under retinal control.[8,48,126,136,165,179,198,219,220,278,360,362,367] Animals exposed to inappropriate light intensity, wavelength, or duration at a given time of day are at major risk for circadian disruption.[37-41,49,52,64,65,74,75,77-85,114-117,125,136,137,141,153,154,181,191,236] The current edition of the *Guide for the Care and Use of Laboratory Animals*[156] (the *Guide*) provides 28 references (21 prior to 1995) associated with light and lighting protocols. The *Guide* cautions that inappropriate lighting and lighting protocols may result in blindness or undue stress in research animals and can distort research outcomes.[27,61] However, the *Guide* provides only limited guidance on how to manage light and lighting protocol concerns and focuses primarily on rodents (particularly Sprague–Dawley rats) based on lighting information available prior to 1985 and knowledge of the primary optic tract and related phototoxic retinopathy studies.[27,61] The *Guide* briefly mentions light's influence as related to husbandry, pigmentation, circadian rhythms, body temperature, hormonal status, reproductive activity, age, species, sex, stock or strain of animals, eating, low-light levels, and cage position.[9,38,39,56,96,130,132,163,239,282,290,292,293,295,297,313,314] Indeed, the current 2011 edition of the *Guide* makes only brief

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mention of the nonvisual system as it pertains to rodents.[28,137] Furthermore, little to no mention is made of the lighting technologies currently in use or even of the rapidly emerging light-emitting diode (LED) technology. In fact, little information is currently available regarding the effects of daytime exposure to LED lighting on either humans or research animals.[77]

The traditional objectives of lighting pertaining to both human and animal physiology and behavior, as stated in the *Guide,* were established by the lighting industry's Illuminating Engineering Society of North America[153,154] and International Commission on Illumination,[64,65] both established in the early 20th century. Their objectives include: (1) lighting must be optimal for visual performance; (2) lighting must permit aesthetic appreciation of space and the environment; (3) lighting must be visually comfortable; and (4) lighting must conserve energy. Generally speaking, the first 3 objectives are reasonably easy to achieve by using any of the technologies currently available, with the current solid-state LED technology arguably being the most versatile, energy efficient and cost effective as compared with other technologies.

The US National Institutes of Health Design Requirements Manual[232] is another resource that is often used by research facilities, particularly for NIH funded intramural and extramural projects. However, the manual focuses on construction-related concerns. That said, the manual specifically states that it follows the specifications established by the Illuminating Engineering Society. These established specifications also apply to the US Department of Energy with regard to community lighting concerns.[333] The general requirements are human-specific and deal with uniformity of lighting, including glare, shadows, unbalanced brightness in the workplace, and vertical surface illumination with light levels determined on the basis of comfort and the visual task involved. The intensity of lighting for humans for offices and research animal housing and support areas ranges between from 270 to 540 lx (110.2 to 220.4 μW/cm^2). Light uniformity is based on human perception of intensity and is measured in lux (illuminance), as a ratio of how light is evenly distributed on the ground compared with the light source above. The closer this ratio is to 1, the more evenly distributed and perceived the light is, and the better the uniformity. Minimum average light levels (with uniformity ratio of 3:1 or lower) are set as follows: animal facilities housing rodents, 270 to 810 lx (110.2 to 330.6 μW/cm^2); animal facilities housing NHP, 540 to 810 lx (220.4 to 330.6 μW/cm^2); facilities housing aquatic species, 540 to 800 lx (220.4 to 330.6 μW/cm^2); animal surgery rooms, 2200 lx (898.0 μW/cm^2); procedure rooms, 1075 lx (438.8 μW/cm^2); cage wash areas, 430 to 540 lx (175.5 to 220.4 μW/cm^2); feed and bedding storage areas: 160 to 270 lx (64.0 to 110.2 μW/cm^2); and facility corridors, 160 to 270 lx (64.0 to 110.2 μW/cm^2). Little to no information is provided regarding fluorescent lighting technology or species-specific lighting (wavelength, intensity, duration requirements); LED lighting technology is only briefly addressed.

This scarcity of information translates to an inability of researchers and animal husbandry personnel to access guidance on how to deal with light and lighting protocol concerns, what to measure, how and why to measure, and what factors to avoid, such as exposure to light at night (LAN). Given that other authors have reviewed the many problems associated with light and lighting protocols in the vivarium,[38,79,102,205] the purpose of this overview is to propose a series of light measurement practices that can provide conservative guidance for facility management and research investigators.

In this review, we discuss the influence of light on circadian rhythms; current lighting industry standards and practices for appropriate light measurement in the vivarium; current understanding of the visual and nonvisual systems; recent findings on the effects of extrinsic light exposure on research animals; evolving light-measurement strategies (metrics), taking into account the complex nonvisual photoreceptive inputs for visual and nonvisual responses to light; and simple recommendations for modifying research animal holding facilities and improving practices to enhance the control of lighting and light–dark cycles. These recommended improvements and practices are conservative and easy to achieve with minimal resources and planning, and are consistent with the best interests of the *Guide for the Care and Use of Laboratory Animals* (the *Guide*),[157] *Animal Research: Reporting of in Vivo Experiments (ARRIVE) Guidelines*,[247] the *Concordat on Openness in Animal Research*,[66] the 3Rs,[281] and the recent NIH mandate regarding reproducibility, transparency, and accountability in research.[63] We further suggest that these improvements and practices should reduce experimental variability, increase reproducibility, reduce the number of animals used, enhance the health and wellbeing of research animals, and improve scientific outcomes.

Light and Circadian Rhythms

All humans and most animal species evolved under a major geophysical event, that is, the rising and setting of the sun. For thousands upon thousands of generations, our bodies were exposed to the presence and absence of light on a daily basis and to the waxing and waning of light through the seasons. Mammals have developed an internal mechanism to respond to light and darkness that is profound in principle and that influences the nervous and endocrine systems throughout the 24-h day (Figure 1). In fact, according to current knowledge, extrinsic light and light–dark cycles regulate in major ways just about every biologic rhythm in mammalian systems from birth to death.[43,136,137,300,344] These mechanisms extend to almost all animals maintained in research facilities around the world. The 4 basic types of biologic rhythms are: 1) circannual rhythms with a cycle of about 1 year, such as migrations and hibernations; 2) infradian rhythms, with a cycle shorter than a year but longer than a day, such as the female menstrual cycle; (3) ultradian rhythms, with cycles shorter than a day, like sleep cycles and eating cycles; and, (4) circadian rhythms, the focus of this overview, which have a cycle of about 24 h daily, such as the sleep–wake cycle, body temperature, and neuroendocrine hormones (e.g., melatonin), as well as many of the other rhythms shown in Figure 1. The advent of electrical lighting technology has disrupted this relationship in both humans and wild animals, and its influence is no less important to animals in the so-called 'controlled' setting of the vivarium. Incorporating the nonvisual effects of light into considerations of vivarium design is likewise important. For example, one might query the extent to which a given architectural design replicates the biologic effects of natural daylight such as the emerging, blue-enriched light-emitting diode (LED) light technology,[77,80,81] how lighting can be used to minimize the deleterious effects of LAN, and how lighting technology can best be employed to enhance the health and wellbeing of research animals.

Current practices for light measurement. The lighting industry, laboratory animal science and biomedical research communities have begun to address many of the issues associated with light, lighting technologies, and light protocols.[77,79.201-205] Progress in these endeavors, however,

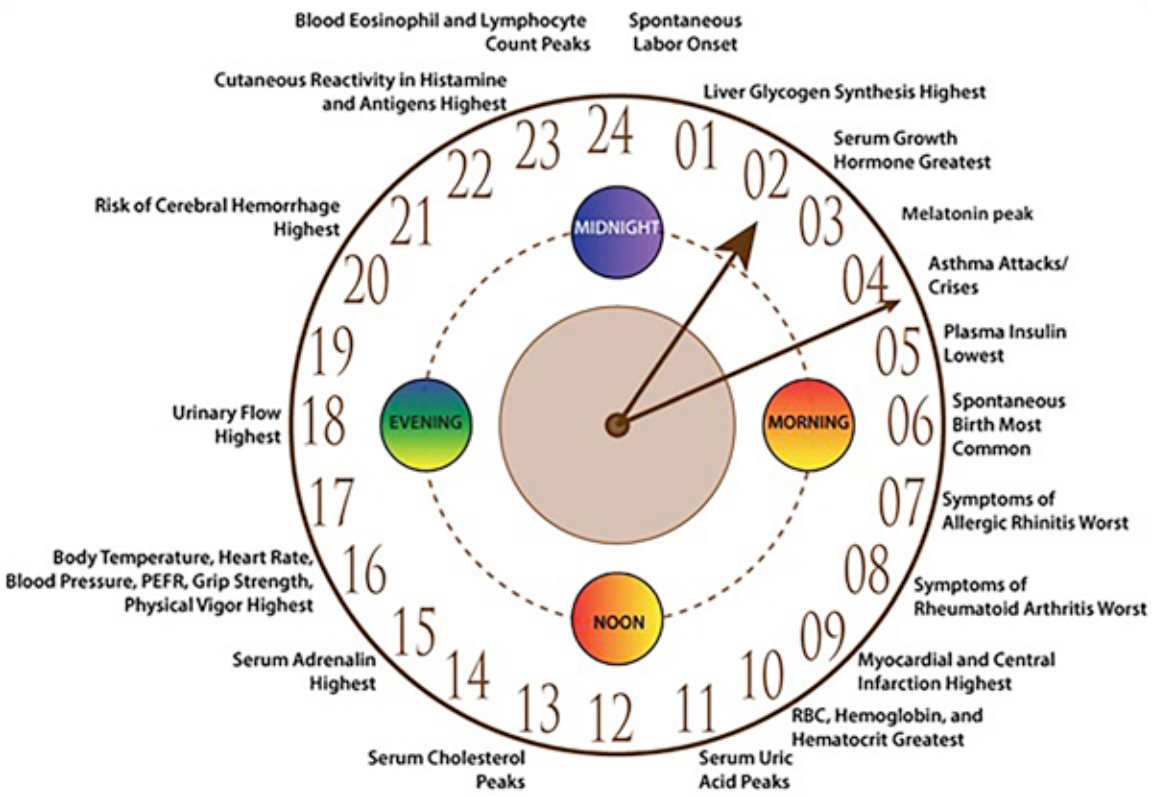

Figure 1. Circadian rhythms with a cycle of about 24 h per day. This figure is presented with permission from the American Association for Laboratory Animal Science.

first requires appropriate quantification of how light affects physiology and behavior. Generally speaking, light measurement techniques fall into 2 categories: radiometry and photometry.[205] Radiometry encompasses the physical properties of light wavelength and energy. A radiometer quantifies radiant power over a defined bandwidth of electromagnetic energy. Photometry is a specialized branch of radiometry that accounts for the fact that biologic photoreceptors are not equally sensitive to all light wavelengths. A photometer is a radiometer that uses filters to weight the detector response to different wavelengths according to the spectral sensitivity of an aspect of animal vision. Most commercially available photometers employ a weighting function, the photopic luminous efficiency function ($\nu\lambda$), which reflects the spectral sensitivity of the long- and middle-wavelength–sensitive cones.[64,65,205] Depending on the geometric properties of interest, luminous intensity (unit of measure, candela [cd; lumens/steradians {lm/sr}]), luminance (cd/m^2), or illuminance (lux [lx; lm/m^2]) can be determined from the output of these devices. During the 1980s through 2000, the vast majority of both human and animal research studies on circadian, neuroendocrine, and neurobehavioral responses to light quantified stimuli in terms of photopic illuminance,[201-205] because light meters that measured in lux were inexpensive and readily available. Two branches of investigation, however, subsequently have shown that this practice is inadequate.

First, during the past 20 y, scientists have learned that although the photoreceptive capacity of the retina is dominated by rods and cones, a small subset of the retina's output neurons (i.e., retinal ganglion cells) also are directly photosensitive (Figure 2).[28,142-144] Most aspects of animal physiology and behavior are influenced by retinal illumination, but they are distinct from the general aspects of vision,[12,13,178,351] because they are not related to spatial patterns of light exposure and persist even in animals that are blind.[204,205,307]

Second, empirical observations have shown that circadian, behavioral, and physiologic responses to extrinsic light have distinct spectral sensitivities. More than 12 analytic spectra and many studies based on selective wavelength comparisons in humans, NHP, and rodents demonstrated that peak sensitivities in the short-wavelength portion of the visible spectrum (447 to 484 nm [blue-appearing]) [28,41,42,202,277,323,366] clearly diverge from that predicted by $\nu\lambda$ (peak sensitivity, 555 nm).

Taken together, these findings indicate that established photometric light measures using the $\nu\lambda$ spectral weighting function, such as photopic lux, are inadequate for quantifying the light that regulates nonvisual physiology and behavior.[156] An alternative method is not currently available; this unfilled need has important ramifications for research animal and biomedical research communities. The lack of an accepted metric—an agreed-upon method—for the measurement of light complicates the comparison of research findings and the replication of experimental conditions. Furthermore, this deficiency hinders the ability of the lighting industry and regulators to predict the influence of various lighting protocols on behavioral and physiologic systems. The fundamental obstacle in addressing this requirement has been the difficulty in determining a spectral weighting function (similar to $\nu\lambda$) for nonvisual responses.[205] Understanding the full scope of this challenge requires a review of our current knowledge of the visual system and, more importantly, of basic neurophysiology of intrinsically photosensitive retinal ganglion cells (ipRGC) and their interactions with the classic rods and cones of the visual systems.

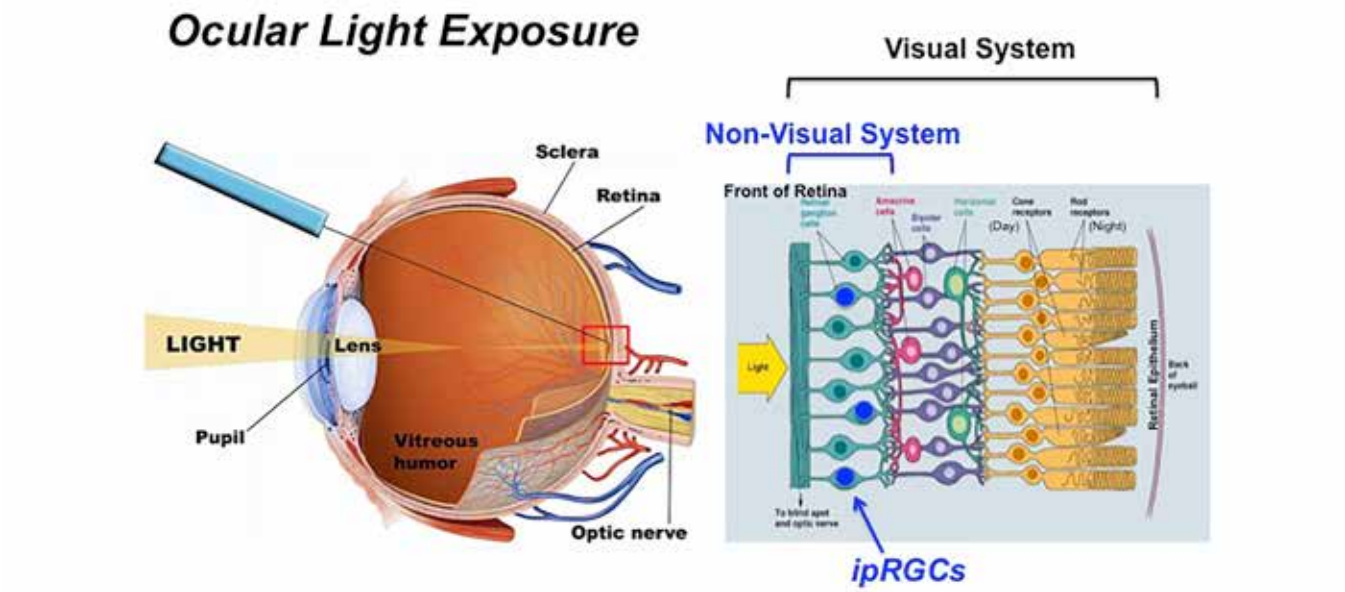

Figure 2. The human retina and eye. The ocular structure of most species follows similar characteristics in both sexes. The retina is a layered structure; light passes through the lens and inner retinal layers (retinal ganglion cells, amacrine cells, bipolar cells, and horizontal cells) to reach the light-sensitive photoreceptors in the outer retina (rods and cones). The retina contains 2 classes of visual photoreceptor: rods, which mediate low-light (scotopic) vision, and cones, which mediate bright-light (photopic) vision and provide color vision. Most mammals have 3 cone opsins, short wavelength (SWS), middle wavelength (MWS), and long wavelength (LWS)–sensitive opsins, except for mice, which have only 2 opsins (SWS and MWS). However, in 95% of cones, these opsins are coexpressed. In addition to rods and cones, a subset of ganglion cells containing the pigment melanopsin, referred to as melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGC), capture light in the blue-appearing portion of the visible spectrum and mediate many nonvisual responses to light. This figure is presented with permission from the American Association for Laboratory Animal Science.

The Visual and Nonvisual Systems

The mammalian visual and nonvisual systems have been investigated extensively in the context of neurobiology and disease (Table 1). Over the past several decades, most of the major advances in our understanding of both systems in responses to light have involved rodents, but all animals used in research share similar ocular architecture and responses, which we summarize here, along with practical recommendations for husbandry and research.

Light enters the eye and passes through the lens to stimulate the retina. The retina is a layered structure, and light must first pass through the inner retinal layer to reach the light-sensitive photoreceptors in the outer retina (Figure 2). The retinal photoreceptor layer of the eye contains rod and cone photoreceptors, which respectively mediate scotopic (low light) and photopic (bright light) vision via the primary optic tract. In most mammals, including nocturnal rodent species (the most widely used for animal research), the retina is rod-dominated, with approximately 6.4 million rods that account for approximately 97% of photoreceptors.[88,182] Conversely, the retina contains only about 200,000 cones, thus accounting for less than 3% of the photoreceptor mileau.[246] Unlike the primate retina, the mouse retina does not have a fovia centralis, or central region, that contains the highest cone density and lacks rods and other neurons. That said, the densities of rods and cones peak in the area centralis, the broad central region that contains fewer receptors than the fovea but more than the peripheral parts of the eye, and decrease peripherally around the retina. Peak rod density in mice is about 100,000/mm^2, whereas peak cone density is approximately 16,000/mm^2, which is comparable to that of humans, NHP, and cats.[182]

The photoreceptor outer segment is the location of the light-sensitive visual pigments, which are transmembrane proteins comprising an opsin protein bound to a light-sensitive vitamin A–based chromophore, 11-cis retinal.[148] Absorption of light photons leads to isomerization of the 11-cis retinal to an all-trans state, resulting in a conformational change in the opsin and allowing activation of the G-protein transducin. Once activated, transducin subsequently leads to activation of phosphodiesterase that, in turn, hydrolyzes cGMP, a serine/threonine-specific protein kinase, into GMP. This step results in the closure of cyclic nucleotide–gated ion channels and hyperpolarization of the photoreceptor cells. Photoreceptor cells are depolarized during the dark phase and constitutively release glutamate, effectively reducing their output signal.[14,103,178]

The retinas of rodents, particularly mice, contain 3 visual pigments: a rod opsin with a peak sensitivity (λ_{max}) at 498 nm and cone opsins that are sensitive to middle-wavelength (λ_{max}, 508 nm) and UV (λ_{max}, approximately 360 nm) light.[47,93,159,160] Due to this UV-sensitive pigment, mice show a greater sensitivity to UV light than do humans.[159,160,310,337] In addition, unlike humans and other mammals, mice lack a long-wavelength opsin and thus are less sensitive to longer wavelength light. A common misconception is that mice cannot perceive red-appearing light in the visible spectrum.[83,246] For example, humans are 12 times more sensitive to a red-light stimulus of 600 nm than are mice.[246] However, this characteristic does not mean that mice cannot detect such light via both the visual and nonvisual systems. When such light is of sufficient intensity and duration, both photoptic systems that regulate the circadian rhythms of metabolism and physiology in mice are quite capable of responding to such long-wavelength light.[83,240,241,246]

The nonvisual system, which consists of the retinohypothalamic tract emanating from the ipRGC of the retina, controls circadian rhythms of metabolism and physiology via light and light–dark cycles. This system was not discovered until 2003 (Figure 2).[28,144] These unique ganglion cells achieve their intrinsic photosensitivity through the expression of the opsin

Table 1. Selected articles addressing the effects of light on animal biology and health

Species	Research areas or effects	References
Homo sapiens	Bright light and melatonin secretion	190
	Light and biologic rhythms	13
	Bright light and the human circadian pacemaker	75
	Monochromatic light and plasma melatonin levels	40
	Light, melatonin, and breast cancer	147
	Melanopsin	257
	Temperature	365
	Action spectrum of melatonin suppression	42
	Shift work, light at night, and breast cancer	86
	Photopigment and melatonin suppression	326
	Light at night and breast cancer	32 and 33
	Phototransduction and circadian clock	28
	Spectral responses and the circadian system	128
	Melanopsin-containing retinal ganglion cells	142–144
	Phase response curves and single bright exposure	168
	Distinct population of intrinsically photosensitive	76
	Melatonin receptors and sleep	95
	Light and neuroendocrine or neurobehavioral regulation	136
	Measuring and using light	205
	Seasonal light circadian entrainment and health	317
	Light exposure devices and nighttime sleep disorder	335
	LED and physiology	243
	Seasonal clock, ulcerative colitis and Crohn disease	107
	Recommendations for light exposure and sleep	49
Macaca mulatta	Light pupillary reflex	256
	Ganglion cells, visual and nonvisual systems	76
	Light or melatonin shifts circadian rhythms	215
	Light, aging of circadian rhythms	370
Callithrix jacchus	Recommended daytime light levels and health	307
Saimiri sciureus	Light and circadian rhythms of locomotor activity	330
Equus ferus	Chronobiology in horses	229
	Light effects on circadian rhythms and health	230
Bos taurus	Melatonin isolation	185
	Effects on neuroendocrine and neurobehavior	196
Sus domesticus	Light intensity, circadian rhythms, and health	132
Capra hircus	Light and reproduction	58
	Light cycles and health	248
Ovis aries	Melatonin analysis	9 and 10
	Photoperiodism and seasonal breeding	30
	Light cycle effects on reproduction and health	237
Canis familiaris	Light and circadian profiles	249
Felis catus	Varying photoperiods and neurohormone concentrations	191
Microcebus murinus	Light and reproduction	187
Mesocricetus auratus	Adrenocortical cytogenesis	270
	Hypothalamic activity of luteinizing hormone and follicle-stimulating hormone releasing hormones	31
	Different light spectra and pineal melatonin	37
	Light irradiance, wavelength, and reproduction	39
	Photoperiod and reproduction	56
	Light and melatonin suppression	255
	Photoreceptors and circadian rhythm entrainment	319
	Light and circadian phase shifting	304
	Photoperiods, circadian rhythms, and depression	29

(*continued*)

Table 1. (Continued)

Species	Research areas or effects	References
Rattus spp.	Constant light and pituitary function	182
	Light and body temperature entrainment	218
	Light and pineal gland serotonin levels	170
	Retinal photopigment that mediates pineal response	52
	Hormonal influence in phototoxic retinopathy	238
	Light and phototoxic retinopathy	27
	Pinealectomy and melatonin suppression	189
	Photoperiodic control of reproduction	234
	Ambient light intensity and melatonin rhythm	208
	Light and phototoxic retinopathy	61
	Light in summer and winter	151
	Diurnal susceptibility to phototoxic retinopathy	96
	Cyclic light threshold and photoxic retinopathy	294
	Light illumination in animal quarters	38
	Preference for low-light intensities	290 and 291
	Phototoxic retinopathy	22
	Phototransduction in ganglion cells	28
	Light effects on heart rate	15
	Animal facility light at night and human cancer growth	78
	Light at night, Warburg effect, and breast cancer	34
	Melatonin suppression of breast cancer	212
	Daytime blue-light exposure and prostate cancer	81
	Degenerative retinal lesions	362
	Daytime LED light and enhanced animal health	80
	Facility lighting and circadian regulation	137
	Melatonin inhibition of multiple diseases	273 and 274
Mus spp.	Low-light intensity preference	346
	Light influence on organ weights	282
	Light and circadian entrainment	98
	Light and genetic control of melatonin synthesis	99
	Melatonin control in various mouse strains	129
	Photoreception in the retinally degenerate mouse	117
	Nutrient preference	16
	Melatonin and metabolism	167
	Phototransduction by retinal ganglion cells	28
	Melanopsin and rod–cone photoreceptive systems	144
	Diminished pupillary response	203
	Light and circadian wheel-running behavior	109
	Diurnal variation and inflammation	213
	Light, rods and cones, and sleep modulation	4
	Light, age, and sleep	140
	Aberrant light impairment of mood and cognitive behavior	184
	Light, melanopsin measurement	205
	Light and feeding behavior	296
	Modulation of memory performance by light	324
	Light and laboratory mice	246
	Facility LAN alters scientific outcomes	102
	Daytime LED light promotes health and wellbeing	77
Octodon degus	Photoperiods and seasonal affective disorders	14
Suncus etruscus	Recommended light levels for healthy maintenance	122
Aves	Photoperiod and circadian rhythms	133
	Photoperiod and endocrine patterns	134
	Circadian melatonin profile	135
	Light, circadian rhythms, and energy	353

(*continued*)

Table 1. (Continued)

Species	Research areas or effects	References
Gallus gallus	Dim light, melatonin, metabolism	1
	Food consumption and growth	51
	LED light and health	197
	Monochromatic light and immune response	361
Reptillia	Light, melatonin, and circadian rhythms	105
	Designing environments, photoperiods, and health	89
	Light and pineal melatonin secretion	224
	Moonlight and behavior	347
	Photoperiods and healthful development	123
Rana spp.	Isolation of melatonin	186
Amphibia	Light, temperature, and body mass	46
	Breeding behavior	19
	Light, circadian rhythms, and health	345
	Light at night and circadian disruption	113
Nauphoeta cinerea	Photoperiod-dependent pheromone suppression	173
Danio rerio	Sleep and regulation	370
	Light-induced gene transcription	348
	Light, gene expression, and sleep	306
	Lighting conditions and gene expression rhythms	92
	Light-entrainable circadian pacemakers	225
	Light, spatial distribution, and swimming behavior	296
	Responses to ambient illumination	298
Leucophaea maderae	Light, circadian oscillations, and homeostasis	253
Drosophila melanogaster	Circadian systems	252
	Molecular genetics, circadian cycling, and behavior	20
	Visual system mutations and circadian rhythms	97
	Light, *Per* gene, and circadian cycling	136
	Light and entrainment of the circadian clock	231
	Light regulation of circadian clocks	115 and 116
	Light and circadian rhythms	367
	Circadian rhythms and feedback loops	278
Onchidium reevesii	Light, circadian rhythms, and memory	362
Eylais extendens	Periods of light and hatching larvae	368
Enterobacter aeroegenes	Circadian clock and light	245

photopigment melanopsin, which absorbs light primarily in the blue-appearing portion of the visible spectrum (564 to 582 nm).[257,258,283] Melanopsin-containing ipRGC comprise only a small portion of the overall ganglion cell population (1% to 5% depending on the species and estimation methodology) but they project to all major portions of the brain via the retinohypothalamic tract, including those with nonvisual responses.[49,100,101,128,138] At least 5 subsets of ipRGC have been identified (4 in the case of nonprimates);[28] their concentrations are species-dependent and have been described to date only in humans, NHP, and rodents.[28,142,143,204,205,246,350] The response to light response of ipRGC is an irradiance-dependent increase in photic activation;, and their downstream responses are activated by much lower levels of illumination than classic rods and cones.[204] Specific ablation of ipRGC only abolishes nonimage-forming responses, identifying this cell class as the principal conduit of photic input to circadian and other systemic responses to light.[49,100,128] Indeed, ipRGC can detect light when isolated from the retina proper, thus explaining why the photosensitivity of these cells survives loss of functional rods and cones[28,114,128,202,366] and why the spectral sensitivity of nonimage-forming responses is different from that of rod- or cone-based vision.[28,74,75,114,202,366]

In all mammals, light provides the principal cue for entraining the circadian system.[161,267] The photoreceptors mediating this process are exclusively ocular, and enucleation eliminates all responses to light.[115,234] However, circadian photoreception, phase-shifting, and suppression of pineal melatonin responses to light are sustained even in the absence of rods and cones and when animals are visually blind.[246] Indeed, all mammals sustain circadian entrainment, suppression of melatonin, and preservation of neuroendocrine and neurobehavioral responses to light via the nonvisual melanopsin-containing ipRGC cells,[257,258] which are directly photosensitive and project via the retinohypothalamic tract to the anterior basal portion of the hypothalamus. The hypothalamus is the site of the suprachiasmatic nuclei (SCN), which comprise the master circadian oscillator in mammals.[28,142] The SCN project over a polysynaptic pathway to the pineal gland, thereby driving a series of molecular events that lead to the production of pineal melatonin (N-acetyl-5methoxytryptamine) primarily at night.[151,221,223] The daily rhythmic melatonin signal contributes

to the temporal coordination of normal behavioral and physiologic functions including sleep–wake,[110,121,199,221,306,315,330,369] cognitive performance,[118] and reproductive[59,265] cycles; immune function;[24,25,54,93,192,209,210,266] gene expression;[55,71,155,325] hormone levels;[87,152,158,164,176,194,233,260,303,321,326,332,340-342] temperature regulation;[110,263,365] electrolyte balance;[119,329] glucose metabolism;[90,188,311,333,334] neural protein synthesis;[18,299] and redox states,[259,271] and melatonin has remarkable antioxidant properties.[323] Although ipRGC can mediate nonvisual responses to light in the absence of rods and cones, functional rods and cones contribute to these responses under normal circumstances. However, if rods, cones, and melanopsin-containing ipRGC are lost, then all responses to light are abolished.[28,242] These responses to light include circadian entrainment and pupillary light responses,[60,120,256] pineal melatonin suppression,[227,228] acute activity suppression,[144] sleep,[5,77,81,84,207,226,250] mood and cognition,[184,324] adaptation of visual pathways,[205,246] and other important responses influencing animal health and wellbeing (Table 1).

The pupillary light reflex (PLR), a well-understood melanopsin-ipRGC–driven response, controls the amount of light reaching the retina by a simple, well-characterized pathway that links a sensory signal and light irradiance to the motor output of pupillary constriction.[60,120,205,219,256,] Data from both animals and humans show that rods, cones, and ipRGC all participate in the PLR and that their contributions are variable depending on light intensity and spectral content; however, the ipRGC are spectrally distinct photoreceptors and their 'firing rate' is sensitive to even a few photons of light, which drives the PLR and ultimately most physiologic and behavioral responses to light.[49,60,120,216,227,256,327,328] This feature is particularly relevant during the vivarium dark phase. At the initiation of the lights-off period, when prior retinal irradiance (from light phase ocular exposure) has exceeded the threshold of melanopsin activation, PLR persists for many seconds into the dark phase. In the presence of LAN in the animal room, both PLR and ipRGC activation may persist. During light phase, this activation is critical for normal circadian regulation of neuroendocrine and neurobehavior parameters associated with animal health and wellbeing. However, animals exposed to light during the dark phase are at high risk of circadian disruption of the central (i.e., SCN) and peripheral clock systems and subsequently to disruptions of physiologic and behavioral circadian rhythms. Although some laboratories[102,108-112,234] have proposed that the nighttime 'dim-light' exposure of one strain of mice is approximately 5 lx (2.0 µW/cm^2), our lab has demonstrated that in several strains of both rats[32-35,79-84] and mice,[77,85] exposure to broad-spectrum cool white fluorescent (CWF) LAN of as little as 0.2 lx (0.08 µW/cm^2) for a period of as brief as 2 h during dark phase is sufficient to disrupt circadian patterns of neuroendocrine and neurobehavioral responses. We discuss this phenomenon more completely in the subsequent section on extrinsic LAN.

Further considerations for vertebrates. Extrinsic light exposure influences SCN regulation of the hypothalamic–pituitary–gonadal axis[169] and significantly influences animal metabolism and physiology, resulting in greater uptake of fatty acids by both normal and neoplastic tissue, reduced lean-to-muscle mass,[145] impaired organ function, and more comorbidities.[57,149] Exposure to light at the wrong time of day (such as LAN) elevates serum fatty acids,[32-35,77-84] body mass, and body fat.[77,112,355,356] Exposing mice to LAN reduces energy expenditure and promotes carbohydrate over fat metabolism, thus increasing body fat mass.[36] Administration of physiologic levels of exogenous melatonin to mice and rats exposed to dim LAN attenuates circadian disruption in adipose tissue.[34,356]

Light modulates glucocorticoid-associated control of an array of biologic functions, including those maintaining homeostasis and physiologic functions.[157,354] These functions include regulation of corticosteroid levels in hamsters,[23] mice, and rats.[111,193,214] Exposure to LAN also affects various physiologic processes that include inflammatory responses, wound healing, blood pressure, growth and development, blood glucose levels, muscle and bone physiology, and mentation.[180,285]

With regard to reproduction, extrinsic light in the vivarium affects the ovaries of species from fish to mammals. Oscillating clock genes in the ovaries are regulated in a defined fashion by light–dark cycles, and misalignment of the circadian clock can alter or inhibit reproduction.[3,6,58,94,195,211,292,352] Reproduction in research species that are seasonal breeders depends on seasonal patterns of light–dark exposure and melatonin production.[269] Indeed, reproduction in photoperiodic animals is compromised by aberrant lighting during dark phase and is highly improved when animal facilities are completely LAN-decontaminated to ensure normal melatonin signaling.

Considerations for invertebrates. Extrinsic light conditions are also a major concern when housing and maintaining invertebrates for research, given that biologic rhythms in these animals, including unicellular organisms, share nearly identical complexity with mammals.[175,338] Indeed, the first clock genes were identified in fruit flies (*Drosophila melanogaster*), work that was awarded the 2017 Nobel Prize in Medicine.[139,278,367] Fruit flies remain a critically important model for the study of genetics, development, and disease.[26,172] Although constant bright light in animal facilities can adversely affect fecundity, longevity, and development in fruit flies,[174,301] little information is available regarding the effect of daytime light (including LED light) on the physiology and metabolism in this species.[2,77,81,84,343] Aberrant lighting conditions may also negatively impact less-commonly studied invertebrates. Exposure to LAN attenuated immune responses in crickets,[102] reduces clutch sizes in ants,[200] and dramatically reduces the likelihood of successful mating in moths, fireflies, and aphids.[106,283,336] Once again, no information is available, as yet, regarding daytime LED technology. Nonetheless, these studies underscore the importance of inappropriate lighting effects, particularly LAN, on circadian rhythms of metabolism and physiology that are highly conserved across species. The use of stable species-appropriate light–dark cycles should always be incorporated into invertebrate housings.

Exposure to extrinsic LAN in the vivarium. Human and animal exposure to LAN is one of the most common events in the community, workplace, and vivarium.[72,73,79,82] Approximately 95% of animals used in research are rodents,[102] but the deleterious effects of exposure to LAN on health and wellbeing apply to all humans and animals. Although rodents have poor visual acuity, they are highly sensitive to light intensity[17] responding to levels as low as 0.2 lx (0.08 µW/cm^2) or less.[79,82] As mentioned previously, exposure of Syrian hamsters to even low levels (15 lx; 6.12 µW/cm^2) of red-appearing 'safety' lights[83] or 0.05 lx (0.02 µW/cm^2) of green-appearing light[255] is enough to disrupt normal nighttime melatonin rhythms, leading to disruptions in other metabolic and physiologic rhythms. Melanopsin-ipRGC, which regulate circadian rhythms of metabolism and physiology in both normal and neoplastic tissues, are highly sensitive to LAN and can be activated by less than 1 lx (0.41 µW/cm^2) of light.[124,125] Clearly, extrinsic LAN in the vivarium, which can originate from light leaking around doors and hallway lights, observation windows, room circuits and electronics, and racks,[82]

disrupts circadian rhythms and triggers a host of metabolic and physiologic effects through 3 key mechanisms: 1) altered expression of clock genes; 2) melatonin suppression; and 3) sympathetic stimulation.[162,183,318,319] Clock genes include brain and muscle ARNT-like protein 1 (*Bmal1*), circadian locomotor output cycles kaput, cryptochrome (*Cry*) 1 and 2, and period (*Per*) 1 through 3—all of which are regulated by light and light–dark cycles and work together to control cellular functions and maintain homeostasis.[243,280,309,318] Disruption of these clock genes by LAN alters feedback loops from the normal 24-h cycle and results in misalignment of circadian rhythms, metabolism, and physiology.[217] Dark-phase exposure to dim LAN for as little as 15 min elevates baseline expression of clock genes, phase-shifts the SCN, and alters phase activity.[254,302,305] Chronic exposure to 5 lx (2.04 µW/cm2) LAN altered circadian expression of *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2* in mice[112] and Siberian hamsters.[25]

The lists of melatonin-receptor–mediated and -independent physiologic functions are extensive.[53,271,272] Alterations in normal melatonin rhythms disrupt endocrine pathways of reproductive, adrenal, and thyroid hormone axes.[289,308,331] Nocturnal melatonin suppression is species-specific and occurs in an intensity-, wavelength-, and duration-dependent manner.[37-45]

Most mammals have robust circadian dark phase melatonin rhythms and pineal melatonin production (Table 1),[267] but this characteristic is not necessarily the case for all strains of mice.[98,99,167] Radioimmunoassay has revealed robust circadian dark-phase melatonin peaks in C3H, CBA [77,129,167,246,312,339] and Foxn1 nude mice,[167,246,339] but such peaks were not found in other inbred strains of mice including C57BL/6, BALB/c, and AKR.[99,129,167] This finding has been debated by investigators who sampled more frequently and thus detected brief nighttime peaks in these 3 strains of mice.[68,210,338] Mutations in enzymes catalyzing the synthesis of melatonin, such as *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase,[166,167,279] may help to explain the variability of melatonin production in various inbred mouse strains. Nonetheless, these mice all maintain robust circadian rhythmicity of other neuroendocrine and neurobehavioral parameters associated with normal light–dark cycles. Indeed, the SCN generate a circadian rhythm in autonomic nervous system signaling that is entrained to the light–dark cycle,[102] independent of the melatonin rhythm, and rodents are 100 times more sensitive to light than are humans.[43] Alterations in sympathetic control can disrupt physiologic processes, including cell cycle control, after changes in lighting parameters;[21] these effects may help to explain in part why some mouse and rat strains are particularly susceptible to various metabolic diseases and cancers.[183]

A large amount of data documents the effects of LAN on cancer in both humans and rodents. The risk of several cancers is significantly higher in industrialized societies that experience circadian disruption in response to nighttime light pollution.[104] Levels of LAN correlate strongly with the development of bre ast,[32-35,85,104,316] prostate, and colorectal cancers.[171,275,287,288,] For more than 30 years, our laboratory has focused its attention on LAN suppression of the pineal nighttime circadian melatonin signal and its effects on normal and neoplastic tissue metabolism and physiology in research animals.[32-35,77-85] Overwhelming evidence to date from our studies and others[67,147,212] demonstrates that circulating levels of melatonin suppress rodent and human tumor proliferative activity in vivo. This suppression occurs via guanine nucleotide-binding protein receptor–coupled MT_1 melatonin receptor-mediated blockade of linoleic acid metabolism to the mitogen 13-hydroxyoctadecadienoic acid via 15-lipoxygenase 1 and aerobic glycolysis (Warburg effect), leading to suppressed activation of the mitogen-activated extracellular signal-regulated kinase p44/p46 (ERK1/2), insulin-like growth factor 1, and serine/threonine kinase signaling pathways. Experimental findings clearly show that exposure to LAN and disruption of the normal nighttime circadian melatonin signal enhances rodent and human tumor linoleic acid metabolism and the Warburg effect to stimulate tumor growth progression.[32-35,78,79,81-83,85,212,268,272,274,275]

Melatonin also can reduce estrogen receptor α mRNA expression or transcriptional activity and aromatase action.[35,222,261] In addition, melatonin can inhibit invasion and metastasis by elevating the expression of adhesion proteins E-cadherin and β1-integrin and reducing that of matrix metalloproteinases.[35,212] This potent neurohormone also counteracts tumor immune invasion by promoting IL2, IL12, and IFNλ production in T cells and monocytes, thus further amplifying oncostatic responses.[53] All beneficial effects of melatonin on cancer initiation and metabolism, progression, and immune cell response are attenuated when animals are exposed to LAN.[34] Whether due to general LAN disruption of circadian rhythms, abrogated circadian nighttime melatonin production, or a combination of the two,, LAN increases cancer risk in humans and animals. As a result of our work and that of others, the International Agency for Research on Cancer (IARC) in 2010 classified LAN, a proxy for shift work, as a probable Class II Carcinogen.[357]

Lighting Technology

Lighting technology can have major effects on the health and wellbeing of research animals.[7,81,83-85] Currently, broad-spectrum CWF lighting in the community, workplace, home and vivaria is the conventional type of lighting used worldwide.[146,154] The Average Rated Lifespan (ARL; or B50) indicates when approximately 50% of the lights will fail in terms of usage in hours. The ARL for CWF lighting is between 8000 and 10,000 h, as compared with older technologies, such as halogen lighting (2000 to 4000 h) and incandescent lighting (450 to 750 h), depending on temperature (indoor or outdoor; temperatures above or below approximately 23 °C). Furthermore, the temporal period of decay, as measured in terms of degradation of light source intensity (lx; µW/cm^2) over time, follows a similar trend, with CWF lighting decay periods that are much longer than those of either halogen or incandescent lighting technologies. This trend also applies to increases in light source vibration and ultrasound over time in the aging process of these lighting technologies.[64,91,137,146] Although CWF light has many advantages over older technologies, such as incandescent and halogen lighting, it also has many drawbacks, including issues regarding disposal (fluorescent lights contain toxic mercury, the disposal of which in regular garbage has been banned by many governments), rapid loss of intensity, elevated noise and vibration, and rapid burn out (2 to 12 y), depending on usage, temperature, and ballast type. Although many of the problems with slow onset, buzzing, and dimming have been corrected, the general population considers CWF light as not being 'warm' or appealing, as with the glow of a fireplace.[153,154] The last consideration can be addressed by using CWF lamps with lower Color Correlated Temperature (CCT) characteristics (that is, 2500 K and lower). The CCT is a perceived visible color characteristic of the light source; generally speaking, light with a higher CCT (above 5000 K) tends to appear more bluish or white-appearing (cool) to the observer, compared with light of a lower CCT (below 1500 to 2500 K), which appears more reddish or yellow-white ('warm').[91]

Institutions worldwide are now rapidly converting from conventional broadband CWF and incandescent lighting to the new LED technology.[73,84,146,154,] More specifically, LED lighting, enriched in the blue-appearing portion of the visible spectrum, is the lighting technology most commonly selected when transitions are needed, because it reflects most closely the full-spectrum of light to which all life has been exposed during evolution over thousands of generations.[4] LED lighting, which now comprises approximately 30% of the current light technology used globally by industrialized nations, is estimated to grow to 80% in usage by 2030.[154] Compared with incandescent or CWF technologies, this new technology is cost-effective, energy-efficient, produces minimal heat and virtually no noise or vibration, has sustained spectral quality, and lasts as long as 40 y without replacement. In addition, LED lighting in the vivarium and workplace is a 'tunable technology,' that is, it can easily be regulated for intensity and spectral quality (wavelength) to provide a wide range of CCT and capabilities for personnel in biomedical research communities. LED convert electricity directly to photons of light, as opposed to the wasteful mixture of heat and light generated by traditional bulbs and lamps (incandescent, CWF) or those that use high-intensity discharge technology, which typically involve electricity–gas discharge using tungsten electrodes and noble gases (mercury vapor, metal halide, sodium vapor, xenon vapor).[64,91]

Another important feature of LED lighting relative to traditional or high-intensity discharge technologies currently in use is that due to its solid-state technology, LED lighting emits little to no high-frequency vibration or noise, including ultrasonic. All of the world's leading manufacturers of LED lamps, which are comparable in size to standard CWF lamps, currently produce a range of lamps that easily fit and function in standard luminaires, so ballasts need not be replaced. Taken together with the remarkable long-term cost and energy savings, these features make it easy to understand why institutions around the world, including vivaria, are rapidly transitioning to LED technology. Indeed, several businesses in the animal research field are rapidly producing and marketing LED-lighted animal biocontainment housing units to meet demand.

Although information regarding the use of LED technology at nighttime in the community, home, and workplace is widespread,[64,65] little to no information is available regarding its daytime use, particularly in animal research settings. In addition, industries related to animal research send many LED products to market without prior studies that validate and support their value in relation to animal health and wellbeing or assess their potential effects on experimental outcomes. Indeed, the little work conducted to date by groups such as the US Department of Energy and the Environmental Protection Agency has focused primarily on the adverse effects of nighttime LED lighting on humans in the community setting, as it pertains to visual glare, sleep disorders, or disruption of various circadian biologic rhythms.[72,73,244] Even the *Guide* currently does not directly include the emerging new LED technology when addressing the topic of lighting technology.

For some time now, our team has investigated exposure to blue-enriched LED light during the light phase (bLAD) in the vivarium setting. Recent IACUC-approved studies from our laboratory revealed that rodents exposed to bLAD, as compared with CWF lighting, and maintained on a static rack systems, had 6- to 7-fold higher circadian nighttime melatonin blood levels, resulting in a marked enhancement on the circadian regulation of neuroendocrine, metabolic, and physiologic parameters associated with animal health and wellbeing.[77,81,84] Subsequent studies by others corroborated these findings in mice[243] and Sprague–Dawley rats[2] maintained on IVC systems. This work provided the first experimental evidence on the influence of bLAD technology on animal health and wellbeing in the vivarium setting.

Recommendations for the Animal Research Community

Regularly monitor, record, and report light measurements. Various vendors currently provide computer-directed lighting sensor equipment to monitor and record animal room lighting intensities during light and dark phases. Unfortunately, in many cases, such sensors have wide ranges of sensitivity, particularly during dark-phase measurements, break down frequently or become inaccurate over time, and even furnish incorrect light–dark cycle information to a central computer source.[102] In some cases, due to a breakdown in the light control or sensing service, computer-generated light–dark cycles are inadvertently altered for weeks without alerting personnel, compromising both animal health and wellbeing and research outcomes. In this regard, we recommend that alarms associated with such computer-directed lighting sensor systems be used to alert animal care personnel (via office or home computer or cell phone) immediately about deviations in animal room lighting protocol concerns; in addition, these backup alarm systems should be monitored regularly. This error typically manifests as lights that remain on during the normal dark phase, rather than as lights that stay off during the normal light phase (a situation that would be noticed by animal care personnel).

We also suggest that animal care personnel and researchers directly and regularly monitor, record, and report light-phase illuminance (lx) or irradiance ($\mu W/cm^2$) levels for the macroenvironment (animal room) and microenvironment (within a cage at eye level) as completely as possible. A variety of low-cost radiometer–photometers are currently available for both older (that is, CWF) and newer (that is, LED) lighting technologies that can collect this information when appropriately calibrated. In effect, this reporting will allow all stakeholders to meet the basic recommendations of the current *Guide* and the ARRIVE guidelines (ARRIVE Essential 10, item 3; Recommended Set, item 15).[247] We further strongly recommend that investigators report the time of day that animal experiments are conducted (that is, surgeries, tissue harvests, treatment regimens) relative to the animal's lights on–lights off schedule, given that time of day significantly affects circadian rhythms of animal metabolism and physiology and experimental outcomes.[31-35,77-85,276]

Minimize variation in vivarium light. The 2 principal elements in light-controlled regulation of animal behavior and physiology are physical–biologic stimulus processing and sensory–neural processing.[137,262] The physical–biologic processing elements are the light source physics, the animal's conscious and reflex behavior in relation to the light source, and the transduction of light to the retina. Factors influencing this physiology include the wavelength sensitivity of the photoreceptors, photoreceptor distribution, photoreceptor adaptation state, and the ability of the CNS to temporally integrate photic stimuli.

Light source geometry relative to the eye is important in understanding the elements of ocular physiology that influence circadian regulation. One measurement technique characterized for architectural lighting[91] and recommended by the *Guide* is to simply place a light meter at 1 m above the floor of an empty animal room, aim it directly at the light source, and measure

light illuminances with the lights on and off. However, this technique may not accurately correspond to corneal illuminance experienced by animals. Clearly, conscious and reflex behaviors including head movement, eye motion, eye blink, and eye closure are important considerations.[120,150,205,246,256]

On the microenvironmental level, with regard to caging, cage type (that is, polycarbonate or polysulfone), wall thicknesses, and location on the rack should all be considered. Nesting materials and enrichment devices may influence circadian rhythms in neuroendocrine and neurobehavioral parameters in rats and mice.[2,77,81.83,359,360] In the vivarium, cage location can markedly influence light intensities. Light intensities are typically greater near the top of the rack[290] but may vary by as much as 80-fold on the same rack and differ by more than 10-fold when measured in the front, middle, or rear of the cage at a given location.[2,77,81,83,343] Cage placement on the rack also affects exposure, as 3 to 19 times more light is available to the top-tier cages compared with those at the bottom of the rack.[62]

Based on our current knowledge (Table 1), we recommend that ambient microenvironment lighting intensities during daytime range between approximately 500 lx (204.1 $\mu W/cm^2$) and 800 lx (326.5 $\mu W/cm^2$) for humans; for domesticated and research animals we recommend a lower range on the order of 100 to 400 lx (40.8 to 163.3 $\mu W/cm^2$). In the case of rodent species, light-phase ocular light intensities in the microenvironment (within-cage) should not exceed approximately 75.0 lx (30.61 $\mu W/cm^2$; average intensity, back-to-front of interior cage environment)[79,80,84,85,363] and should be lower when feasible.[136,137,205,246] In addition, the lighting technology should provide diffuse daytime lighting, that is, more blue-appearing (in the visible spectrum), with the objective of healthful exposure of both the visible (rod, cone) and nonvisible (melanopsin-ipRGC) photoreceptor systems to known thresholds of different biologic responses to light, including entrainment of the circadian clock, pupillary constriction, regulation of neurohormones such as melatonin and corticosterone, and modulation of sleep and cognition.

Furthermore, nesting materials and enrichment devices can provide physical barriers between animals and light sources but can also alter animal physiology and metabolism.[358,359] This situation sets the stage for significant interanimal variability as well as potential changes in retinal morphology[130] that may confound toxicity studies.[262]

Options for minimizing light variation in cages include using similar location for all cages on a given study, rotating cage position on the rack to counter subtle—or not so subtle—changes in cage position on the rack, or employing specially-designed photobiologic light cabinets that deliver consistent lighting to all cages. Some investigators use small spaces or cubicles and place lamps in corners, which may result in more consistent illumination. In most cases and during specific investigations, cage racks can be placed appropriately under luminaires to deliver similar external light intensities to different units. In addition, cage material, bedding, and enrichment devices modulate the amount of light available to the animals.[358] We recommend a few considerations for the use of small animals such as rodents: (1) minimize the number and type of enrichment devices per cage; (2) be cognizant of the type of enrichment devices employed; (3) be consistent during and between studies with regard to type/number of enrichment devices employed; (4) maintain this consistency between control and experimental animals; and, (5) continue to report macroenvironmental (room) and microenvironmental (within cage) lighting intensity illuminance and irradiance measures (at eye level) in the interest of experimental reproducibility, accountability, transparency, animal health and wellbeing, and scientific outcomes.[63,77,81,84,359] For short-term studies, some investigators may simply remove all enrichment devices, with IACUC approval. Recent studies have shown that the spectral transmittance of light passing through standard rodent cages (polycarbonate or polysulfone) of different tints significantly influences circadian metabolism and physiology in commonly used rodent strains.[80,358] Further elucidation of the specific ocular and neural elements mediating these biologic effects of light in mammals, particularly in determining the interdependence and variability, remains an emerging science.[43,115,205]

Cage rack technology (that is, static, IVC, or emerging biocontainment technology) may be important when using either CWF or LED lighting during the light phase.[2,77,343] Whereas animals maintained on static or IVC systems are exposed to either diffuse, broad-spectrum CWF or LED lighting from overhead luminaire systems (that is, tubular, or 'T' designated lamps), animals maintained in the new biocontainment units are subject to LED strip lighting that varies, depending on the manufacturer, in their location within the unit. Animal ocular light exposure is linear across the cage unit and not as diffuse, and light photons excite the visual rod–cone and melanopsin-ipRGC systems differently.[205,246] How this situation translates to potential circadian rhythm alterations in neurobehavioral and neurophysiological parameters has only been recently investigated.[2,77,81,83,131,343] These studies revealed that although most strains of rats[80,81] and mice[77] maintained on either static units or IVC units[343] in translucent, clear polycarbonate cages and exposed to bLAD, compared with CWF light, had significantly higher plasma melatonin levels and lower body growth rates, food and water intake, and plasma circadian markers, this was not completely the case for blood serum chemistry panels in one strain of rats maintained in a newly manufactured and marketed LED-lighted biocontainment system. That acute, short-term study only replicated elevated circadian nighttime melatonin blood levels and some blood analytes.[2] What was clear from these studies[2,343] is that bulb type and technology can both influence circadian rhythms. Nonetheless, LED light in general also exerts broad effects on the circadian regulation of neuroendocrine, metabolic, and neurobehavioral parameters associated with the promotion of animal health and wellbeing and may influence scientific outcomes. Despite variations in the type of light exposure and spectral quality due to the various aforementioned parameters, all should be standardized in experiment design and fully reported in research publications.

Another consideration regarding the rapidly emerging 'tunable' LED technology is the use of gradual changes in light-phase and dark-phase onsets, emulating natural dawn and dusk periods.[102,205,246] In other words, at the onset of light phase, light sources can gradually increase in intensity from 0 to 400 lx (room measures) and in spectral quality from longer wavelength (red–yellow) to shorter wavelength (blue-enriched) over a brief period (for example, 3 to 5 min). Conversely, at the onset of the dark phase, animal room lighting can be adjusted in reverse fashion for decreasing intensity (from 400 to 0 lx, room intensity) and increasing wavelength (blue-enriched to red–yellow-enriched to total darkness [0 lx]), thus more emulating the natural nighttime transition. Some rodent studies have shown that these gradual photoperiod transitions may reduce stress and positively influence animal health and wellbeing.[25,109,111,112]

Eliminate LAN pollution in vivaria. The *Guide* recommends the elimination or limitation of extrinsic light exposure during the dark phase and the use of a time-controlled lighting

system to guarantee regular cycling, with light cycles set at intensities previously described.[156] Despite these recommendations, vivarium lighting is often adjusted to meet the needs of both animal care and research personnel. Brighter room lights are often used during cage changing or room cleaning to aid in visualization; dimmer intensities may be used during the remainder of the light phase, when personnel are not present. These photic disturbances, including entering and exiting rooms from a common lighted corridor during dark phase and using observation windows, even when covered with red safety filters, alter animal ocular light exposure, the degree to which this occurs also depends on cage and rack location in the LAN-contaminated animal room.[83]

For many years, our Tulane Center for Circadian Biology team has investigated the influence of light, particularly LAN, on human and animal metabolism and physiology. Although the role of light in vision is widely recognized, our studies have focused on the role of light in nonvisual responses, including entrainment of circadian rhythms and regulation of neurohormones and neurobehavior. More specifically, our NIH- and AALAS GLAS-supported studies provided the experimental evidence in support of the epidemiologic findings[86,211,287,288] in the night shift work population regarding the association between LAN and invasive breast cancer risk.[1,25,78,79,85,331] As mentioned above, night-shift work, emulating LAN and circadian disruption, is currently classified as a Class IIA probable human carcinogen by the World Health Organization and the International Agency for Research on Cancer.[357]

In view of these considerations, we recommend the elimination of all dark phase extrinsic LAN in the vivarium. As discussed earlier, LAN-induced suppression of endogenous melatonin production may promote various disease processes, including carcinogenesis and metabolic syndrome.[32-35,78,79,81,82,85] LAN contamination in animal facilities is a common problem, even in modern facilities; however, simple remedies are available for many common sources of LAN contamination. To ensure maintenance of complete darkness in animal facilities, animal holding rooms should be inspected for sources of light pollution, and room entrance during dark phase should be controlled to prevent unwarranted light intrusion. A host of cost-effective data loggers and alarm systems can be used to monitor animal facility light intensities and lighting alarm systems can be used to detect unwanted light and inappropriate entry during dark phase. Although one set of recommendations may not be optimal for all animal uses, important considerations to insure complete darkness during dark phase include: 1) removing unnecessary lighted equipment; 2) covering light sources in animal rooms, including electronic indicator lights, ventilated tower screens, and circuits; 3) eliminating animal observation windows on doors or completely covering them with blackout shielding; 4) installing door frame shoes, seals, and sweeps with vinyl gaskets and anodized aluminum encasements; and 5) installing light-tight, black-out curtains. These modifications can be remarkably effective. When possible, entry into main animal holding quarters from an unlighted LAN-decontaminated internal room, as compared with the outside lighted corridor, is also an excellent option for consideration.[79]

Finally, with regard to the use of red safety lights, some animal species, including mice and rats, have been suggested to be insensitive to red light.[102] Although partially true, insofar as the visual system is concerned, numerous studies detailing irradiance response curves to long-wavelength light (> 600 nm) demonstrate sensitivity to red light if the intensity and duration are high enough.[50,144,205] Using dim red safety light(under 35 lx; 14.3 μW/cm^2) for under 15 min during dark phase, to include red safety flashlights, is an effective alternative to maintain circadian organization in research animals.[83] However, all red-appearing lights do not emit solely in the red spectrum and may not exclude all shorter wavelength light. We recommend using a photometer to confirm emitted wavelengths prior to use. As a result of this misunderstanding of photobiology, a simple solution for the problem has been to use reverse lighting in animal facilities and red light or sodium light (589 to 590 nm), which will allow humans to see but is on the margins of rodent sensitivity.[246] For example, the known visual pigments of the mouse retina are around 12 times less sensitive than humans to 600-nm red light and around 8 times less sensitive to 589-nm sodium light. As such, the level of nocturnal light required for humans to work in a mouse room for a sustained period of time would certainly produce nonvisual biologic responses in mice. With this situation in mind, we recommend only limited use of these light sources (below 35 lx [14.3 μW/cm^2] for less than 15 min) in the vivarium during the dark phase.

Apply the new metric for measuring and using vivarium light. The inadequacy of a consistent and accepted method of quantifying light complicates the replication of experimental conditions and comparisons across studies, thus hindering scientific advancement. The scientific literature contains a substantial number of investigations relating circadian, neuroendocrine, and neurobehavioral responses to calibrated light exposure. Light influences all life on the planet in an intensity-, duration-, and wavelength-dependent manner.[37-40] That said, many studies do not provide any information on animal facility light levels, light spectral quality, or even light–dark lighting protocols other than saying that they conform to local regulations. Such regulations typically are based on the level of light required for staff to work rather than on consideration of animal physiology.[246]

When light measurements are provided, they are invariably expressed in lux (lx), a unit based on perceived brightness according to the sensitivity of the human visual system. In addition, the lux measurement unit is based on the photopic (daytime) sensitivity curve, which has a peak sensitivity of about 555 nm, reflecting the red (middle wavelength) and green (middle wavelength) cones of the human retina. This unit of measurement is not relevant for most animal species, including rodents, because it does not reflect scotopic (nighttime) responses, when rods provide the primary responses to light, nor does it provide any reflection of the important melanopsin-ipRGC contributions to nonvisual responses. Instead of using such units, radiometric units based on unweighted power measurements (μW/cm^2) are more relevant and are preferred in circadian biology.[115,205,246] We highly recommend providing the type of lighting (that is, incandescent, CWF, or LED) so that radiometric approximations can be made and reported. Once again, for most research species of interest (Table 1), light-phase light intensities in the macroenvironment (that is, outside of housing, caging, or aquarium environments) should not exceed approximately 325 to 400 lx (132.7 to 163.2 μW/cm^2), as is currently recommended by the *Guide*, and dark-phase light intensity levels should strictly be maintained at 0 lx (0 μW/cm^2; no LAN). With regard to the microenvironment (that is, within the housing, caging, or aquarium environments) for most species, particularly for rodents, light-phase ocular light intensities should not exceed approximately 75.0 lx (30.61 μW/cm^2),[79,80,84,85] aiming for the side of lower intensities. Equally important is using equipment that accurately measures these

intensities, which should be recorded and reported regularly in the interest of animal health and wellbeing and researcher accountability, transparency, and experimental reproducibility.[63]

Due to the lack of an accepted spectral weighting function for nonimage-forming responses to light, we also suggest the recording and reporting of corneal spectral power distributions based on species-specific action spectra data.[69,70,205] Again, a range of low-cost spectroradiometers are commercially available for this purpose. The advantage of recording and reporting spectral power distributions is that the data can be used to derive any unit of measure at the time of collection or in the future. Currently, such data are used to calculate effective irradiance experienced by the various rod, cone, and melanopsin-ipRPG driving nonvisual input responses and facilitates overcoming the problem of comparing polychromatic light of different spectral qualities. Full equations for calculating all species-specific (including rodents) visual and nonvisual system opsin illuminance values (rhodopic, melanopic, cyanopic, chloropic, and erythropic) are available in the Peirson Toolbox.[235]

As mentioned above, the *Guide* incorporates the traditional objectives of lighting set forth by the International Commission on Illumination and the Illuminating Engineering Society for vivarium design and lighting that are optimal for visual performance, visual comfort, permit aesthetic appreciation of the space, and energy savings.[64,65,154] As we have discussed, light exposure profoundly influences numerous physiologic and behavioral effects. We argue that the nonvisual effects of light should be controlled in the design and operation of human environments and those of research animals.

Balancing the desirable and undesirable effects of light and darkness requires careful, comprehensive consideration of context and the multitude effects of light on perception, neurophysiology, and neurobehavior. Although prediction of the nonimage-forming effects of a given light source is not currently feasible based on its intensity and spectral composition, some guidance is possible. If the objective is to minimize activation of melanopsin ipRGC, the goal should be to keep retinal irradiance as low as possible during the dark phase, keeping in mind that any light wavelength can, in principle, activate the system.[205] Conversely, during the light phase, if the objective is to promote melanopsin-ipRGC photoreception, retinal irradiance should be raised (within safe limits) and light sources should be biased toward the blue-appearing portion of the visible spectrum, to which all inputs are very sensitive. Our previous investigations [77,79,81-83] support this latter course of action with regard to bLAD exposure.

Conclusions

Light exerts profound effects on animal physiology and behavior. Much like noise, vibration, temperature, humidity, air, and water quality, among other factors, light is considered to be one of the major extrinsic factors in an animal facility that significantly influence animal health and wellbeing. Extrinsic factors like light act on the animal and may alter intrinsic factors that include genetics, circadian rhythms, age, sex, and immune and endocrine status. Whether from conventional or emerging new technological sources, such as LED lighting, light influences our circadian system in an intensity-, wavelength-, and duration-dependent manner, and consistent light exposure is critically important to animal health and wellbeing.

Biomedical research, including the use of animals, and engineering rely on accurate measurement and reporting. The discovery of the melanopsin-ipRGC photoreceptors and our growing understanding of their role in regulating animal physiologic and behavioral states have demonstrated that the current methods of light measurement and reporting are no longer adequate. How they should be updated is a question that remains and will no doubt be revisited as our understanding of this system evolves. Nonetheless, the science has now reached a state that makes it sensible to take important steps forward in this process. Understanding the effects of light on animal physiology, metabolism, and behavior must incorporate the effects of the visual and nonvisual photoreceptor systems function, including their differing sensitivities to light intensity, wavelength, duration, how they interact, lighting technologies, and a wide range of species-specific differences. To this end, our overview of the influence of light on circadian rhythms, current industry standards for appropriate light measurement in the vivarium, the visual and nonvisual systems, simple recommendations for improving the control of vivarium light–dark cycles, and appropriate recording and reporting light measures provides basic foundations on which future developments can build. The consistency and quality of lighting intensity, wavelength, and duration during controlled photoperiods are of utmost importance in maintaining normal, healthy animal biologic rhythms of metabolism and physiology and in influencing the outcome of scientific investigations. We, therefore, encourage the research animal science and biomedical research communities to be cognizant of the influence of light, lighting technologies and lighting protocols on both the remarkable animal 'heroes' that we care for and use and on our own day-to-day lives.

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